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Intestinal angioedema caused by an acquired C1 esterase inhibitor deficiency associated with underlying splenic marginal zone lymphoma

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ABSTRACT

A 75-year-old woman presented with recurrent abdominal pain and vomiting for 1 year and was later found to have splenomegaly and pancytopenia. This case report depicts a clinical picture of intestinal angioedema, a challenging diagnosis, and an underlying rare syndrome of acquired C1 esterase inhibitor deficiency associated with splenic marginal zone lymphoma.

KEYWORDS C1 esterase inhibitor deficiency; intestinal angioedema; splenic marginal zone lymphoma

Unlike cutaneous angioedema, intestinal angioedema is a challenge to diagnose, as patients typically present with nonspecific acute abdominal pain, vomiting, and diarrhea. Low awareness and resemblance to other disorders of C1 esterase inhibitor deficiency acquired angioedema (C1-INH-AAE) often delay the diagnosis[1] or even lead to unnecessary surgery.[2] We report a case of splenic marginal lymphoma (SMZL) presenting with recurrent intestinal angioedema from C1-INH-AAE before the manifestation of splenomegaly and pancytopenia to raise awareness among physicians about this rare disorder as a cause of recurrent abdominal pain.

CASE PRESENTATION

A 75-year-old white woman with hypertension and hypothyroidism presented with recurrent sharp abdominal pain, bilious vomiting, and constipation for 1 year. She was diagnosed with multiple episodes of partial small bowel obstruction, which responded to conservative management. She reported two episodes of swelling in the face, hands, and feet. She had lost 20 to 30 pounds over 3 months. The enlarged spleen was palpated at 6 cm below the left costal margin.

Contrast-enhanced computed tomography (CT) of the abdomen and pelvis showed splenomegaly (16.1 cm) with splenic varices and bowel wall thickening with mucosal enhancement suggestive of enteritis *(Figure 1)*. Small bowel enteroscopy showed jejunal narrowing at 70 cm distal to the pylorus without signs of inflammation; the biopsy result was normal. Colonoscopy was unremarkable. The FibroScan score was 7.7 kPa. A complete blood count showed pancytopenia, with white blood cells 2.89 k/μL, hemoglobin 9.3 g/dL, mean corpuscular volume 84.3 fL, and platelet count 96 k/μL. A peripheral blood smear showed pancytopenia with no atypical cells. The complement component 4 level was low at <6 mg/dL (normal 10–40 mg/dL), C1-INH protein level was low at 4 mg/dL (normal 21–39 mg/dL), and C1-INH protein function was low at 18% (normal ≥68%). An antinuclear antibody test was negative. Peripheral blood flow cytometry revealed a small population (0.1%) of monoclonal B cells with nonchronic lymphocytic lymphoma type, with no evidence of an aberrant T-cell process or increased blasts. Bone marrow biopsy revealed a hypercellular marrow (60%) with megakaryocytic hyperplasia but no evidence of B-cell lymphoma involvement. Fluorescence in situ hybridization was negative for abnormalities of chromosomes 3, 7, 11, 18, rearrangements of BCL6, MALT1, or t(11;14) translocation. The cytogenetic result was normal (46, XX).

With high suspicion of splenic lymphoma as the cause of splenomegaly and acquired C1-INH deficiency, splenectomy

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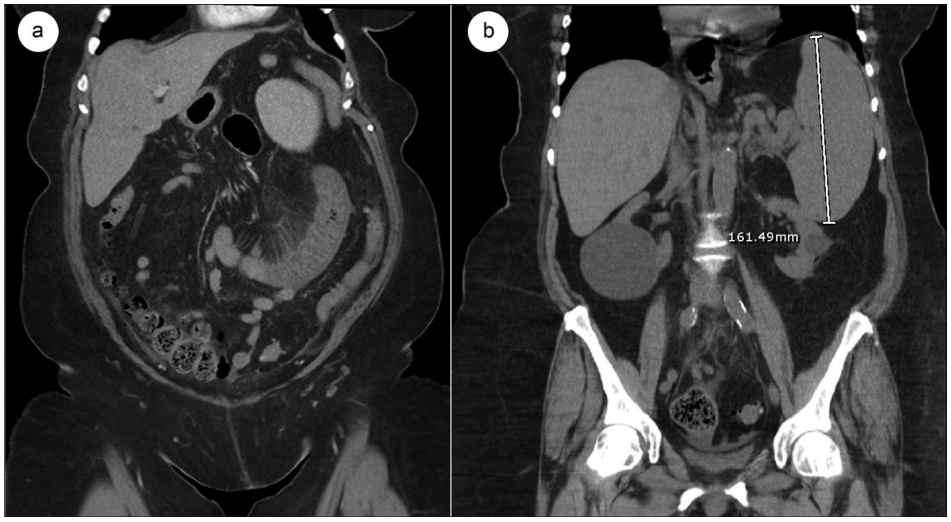

Figure 1. Contrast-enhanced CT of the abdomen and pelvis demonstrating **(a)** jejunal wall thickening with mucosal enhancement, clear delineation of different layers of bowel wall, and prominent mesenteric vessels, and **(b)** splenomegaly (16.1 cm) with splenic varices and renal cysts bilaterally.

was done for diagnostic and therapeutic purposes. The pathology of the spleen showed a small B-cell population with morphologic and immunophenotypic features consistent with SMZL expanded in the splenic white pulp. Immunohistochemistry was positive for CD20 and BCL2 and negative for CD5, CD10, and BCL6. A clonal immunoglobulin heavy chain rearrangement corresponding to monoclonal B-cell proliferation was detected by polymerase chain reaction. *BRAF* V600E mutation was negative. The patient recovered from the surgery well and had not experienced any episodes of angioedema or related symptoms at 3-month follow-up.

DISCUSSION

C1-INH-AAE is a rare syndrome causing recurrent episodes of self-limited angioedema localized to the upper respiratory tract, gastrointestinal mucosa, and subcutaneous tissue without urticaria[3] in those >40 years with no family history of angioedema.[4] Contrast-enhanced abdominal CT scan can help diagnose intestinal angioedema by demonstrating bowel wall thickening with mucosal enhancement, clear delineation of different layers of the bowel wall, prominent mesenteric vessels, fluid accumulation in bowel loops, and ascites during the angioedema attacks. The resolution of these findings on repeated imaging supports the diagnosis.[5]

Eighty-five percent of patients with C1-INH-AAE have an underlying disease of lymphoproliferative disorders, monoclonal gammopathies of undetermined significance, B-cell malignancies, autoimmune disease, adenocarcinoma, and other malignancies.[3] Despite its rarity, SMZL has a higher prevalence (66%) in C1-INH-AAE patients with non-Hodgkin lymphoma than other patients with non-Hodgkin lymphoma (2%).[6] It was proposed that clonal B-cell proliferation in SMZL leads to the production of C1-INH-neutralizing autoantibodies.[6] The loss of inhibitory control of the kallikrein-bradykinin pathway and classical complement pathway caused by low levels of C1-INH then results in attacks of angioedema.[7] The clinical manifestations of angioedema may precede and hinder the diagnosis of a lymphoproliferative disorder for years, as in our case. Clinicians should be aware of these conditions, as screening and treating underlying disease properly often result in partial or complete remission of C1-INH-AAE.[6]

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